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Etiologic and demographic characteristics of patients with anisocoria

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Abstract
Aim: In this study, we aimed to present the etiological causes and clinical features of the patients followed for anisocoria and to determine the most common causes according to age groups.
Material and Methods: The medical records of the patients aged 18 years and over who were followed up for anisocoria between June 2017 and December 2022 were retrospectively reviewed. Two groups were formed including patients aged 18-45 as Group 1 and patients over 45 years old as Group 2. The etiological causes were divided into 4 groups as physiological anisocoria, pharmacological anisocoria, ocular pathologies and nervous system pathologies. It was examined whether there was a difference between the two groups in terms of four main etiological reasons.
Results: A total of 99 patients followed for anisocoria between January 2017 and December 2022 were included in the study analysis. The most common cause of anisocoria was found to be due to ocular pathologies (64 eyes, 64.6%). The second most common etiologic cause was found to be physiological anisocoria (20 eyes, 20.2%). Anisocoria was observed in 12 (12.1%) patients due to neurogenic dysfunction and in 3 (3%) patients due to pharmacological effects. There was no statistically significant difference between groups 1 and 2 according to etiological causes (p=0.089).
Discussion: The ocular pathologies were found to be the most common cause of anisocoria. The most common ocular causes detected also varied in parallel to demographic changes. There is a need for descriptive studies of the etiology of anisocoria with a higher number of participants.

Keywords
Anisocoria, Parasympathetic System, Pupil Diameter, Sympathetic System, 3rd Cranial Nerve

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Introduction

Anisocoria is defined as a difference between two pupil diameters greater than 0.1 mm [1]. Benign causes such as physiological anisocoria can take place in the etiology of anisocoria, as well as life-threatening causes such as intracranial mass can be seen [2]. As in many diseases, first of all, a detailed anamnesis should be collected from the patient. The probability of a long-standing anisocoria is much less likely to represent a dangerous medical condition than a sudden onset of anisocoria. Therefore, it is necessary to question how long anisocoria has been present. Medical conditions such as medications used by the patient, history of eye and cranial trauma, and history of eye surgery should be questioned. After collecting a comprehensive anamnesis, an abnormal pupil needs to be identified. Changes in anisocoria to light provide valuable information about the underlying pathology. Since the pupil is dilated in the dark, anisocoria, which becomes more prominent in the dark, indicates that the smaller pupil is abnormal and points out that there is a problem in the sympathetic pathways. Since the pupil is required to shrink in the light, the larger pupil in the anisocoria that becomes evident in the light is abnormal and makes us think of a problem in the parasympathetic pathways [3].

Systemic and topical drug use, headaches, trauma, ophthalmologic diseases, autonomic ganglion pathology, and intracranial diseases are among the potential etiologies of anisocoria [4,5]. Since anisocoria can be an important clinical finding of nervous system dysfunction due to causes such as intracranial hemorrhage, cerebral neoplasm, aneurysm, and meningeal infiltration, it should be evaluated urgently and the underlying pathology should be revealed [4]. Literature studies of anisocoria are generally presented in the form of case reports. In our study, the etiological causes and clinical features of the patients followed for anisocoria were presented and the most common causes according to age groups were tried to be determined.

Material and Methods

This descriptive study was conducted retrospectively. The study was approved by the local ethics committee (Date: 26.01.2023, no: 7/2023) and was conducted in accordance with the Declaration of Helsinki.

The medical records of patients aged 18 years and over who were followed up for anisocoria between June 2017 and December 2022 were retrospectively reviewed. The demographic characteristics of the patients such as age, gender, comorbidities and underlying etiological causes were analyzed. Two groups were formed: patients aged 18-45 years were included in Group 1 and patients over 45 years old were included in Group 2. The etiological causes were divided into 4 groups: physiological anisocoria, pharmacological anisocoria, ocular pathologies and nervous system pathologies.

Physiological anisocoria is a clinical condition in which the pupillary difference is usually 0.4-1.0 mm and this difference remains constant in dark and light, and there are no ophthalmological and neurological pathologies [6,7]. Pharmacological agents can cause both mydriasis and miosis. Ocular traumas and previous ocular surgeries, congenital anomalies, pseudoexfoliation syndrome (PES), iris disorders are the most common causes of ocular anisocoria. Aneurysms, intracranial hemorrhages and space-occupying lesions that cause 3rd cranial nerve (3rd CN) dysfunction can lead to parasympathetic nervous system dysfunction [1]. Hypothalamus lesions, spinal cord lesions, and carotid dissection, lung and thyroid diseases that can affect the cervical ganglia impaire the sympathetic discharge and thus a dysfunction in mydriasis can occur [1]. After our study patients were grouped into 4 main groups etiologically, the causes constituting each group were examined in detail. Ocular pathologies were grouped as congenital anomalies, iridocyclitis, traumatic iris defects, surgical iris defects, acute glaucoma crisis, benign episodic mydriasis, Adie's tonic pupil, and PES. Causes causing neurogenic dysfunction were grouped as intracranial hemorrhages, intracranial masses, congenital 3rd CN pathologies, traumatic 3rd CN paralysis, non-traumatic 3rd CN paralysis (infection, inflammation, vascular, etc.), posterior communicating artery aneurysm and cervical ganglion and/or sympathetic nerve pathway pathologies.

It was examined whether there was a difference between the two groups in terms of 4 main etiological reasons. In addition, differences of the causes causing ocular pathologies between the two groups were statistically analyzed. A comparison between the 2 groups could not be made due to the very low number of patients having anisocoria depending on the neurogenic causes.

Statistical analysis

Data analysis was analyzed using SPSS version 25. Descriptive data were presented using mean, median, and percentage as appropriate. Differences in etiological factors between the two groups over 45 years old and under 45 years old were examined using the Pearson chi-square test. We considered $p < 0.05$ to be statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 99 patients followed for anisocoria between January 2017 and December 2022 were included in the study analysis. Of 99 patients, 45 were female and 54 were male. The mean age of the patients was 49.97±21.57 years (range 18-88 years). The most common cause of anisocoria was found to be due to ocular pathologies (64 eyes, 64.6%). The second most common etiologic cause was found to be physiological anisocoria (20 eyes, 20.2%). Anisocoria was observed in 12 (12.1%) patients due to neurogenic dysfunction and in 3 (3%) patients due to pharmacological effects (Table 1).

There were 43 patients in Group 1, aged between 18-45 years, including 15 female patients and 28 male patients. Anisocoria was detected due to ocular causes in 22 patients, neurogenic dysfunction in 8 patients, and pharmacological effects in 2 patients. Physiological anisocoria was found in 11 patients. There were 30 female and 26 male patients in Group 2 (over 45 years old). The mean age was 66.84±10.48 (47-88) years. Similar to Group 1, ocular causes were seen in 42 (42.4%) patients and were found to be the most common cause. Physiological anisocoria was observed in 9 (9.1%) patients, and neurogenic dysfunction was observed in 4 (4%) patients.

Pharmacological effects were observed in 1 (1%) patient in this group (Table 1). The most common and rarest etiological factors were found to be similar in both groups, and there was no statistically significant difference between the groups (p=0.089).

When the ocular pathologies causing anisocoria in Group 1 were examined among themselves, it was seen that the most common cause was trauma-related iris and sphincter defects (n=7, 7%). Congenital anomalies of the iris were found to be the second most common cause (n=6, 6%). Iridocyclitis was detected in 5 patients, surgical iris defects in 2 patients, and glaucoma crisis in 2 patients. PES, benign episodic mydriasis and Adie's tonic pupil were not observed in Group 1.

The most common cause of anisocoria in Group 2 was iris defects secondary to ocular surgeries (n=16, 16.1%). There were glaucoma crises in 10 patients, PES in 7 patients, iris and sphincter defects due to trauma in 7 patients, and uveitis in 2 patients. Congenital anomalies of the iris, benign episodic mydriasis and Adie's tonic pupil were not observed in Group 2. When the distributions of ocular pathologies were compared between the two groups, it was found that the two groups were statistically different from each other (p=0.000) (Table 2).

When the distribution of neurogenic pathologies causing anisocoria was examined in Group 1, the most common cause of the 3rd CN paralysis due to trauma was found. (n=4, 4%). Posterior communicating artery aneurysm was seen in 2 patients and intracranial hemorrhage was seen in 2 patients. In Group 2, 2 patients had intracranial hemorrhage, 1 patient had an intracranial mass, and 1 patient had nontraumatic 3rd CN palsy.

Table 1. Distribution of etiological causes of anisocoria according to groups.

	Group 1 (18 to 45 years)	Group 2 (45+ years)	p
	f/m	f/m	
Ocular Pathologies	22 (22.2%) 7/15	42 (42.4%) 24/18	0.089*
Physiological Anisocoria	11 (11.1%) 4/7	9 (9.1%) 4/5	
Neurological Pathologies	8 (8%) 2/6	4 (4%) 2/2	
Pharmacological Anisocoria	2 (2%) 2/0	1 (1%) 0/1	

f/m: female/male *: Pearson chi-square test

Table 2. Distributions of ocular and neurological pathologies causing anisocoria.

		Group 1 N (%)	Group 2 N (%)	p
Ocular pathologies	Trauma-related iris and sphincter defects	7 (7%)	7 (7%)	0.000
	Congenital anomalies of the iris	6 (6%)	-	
	Surgical iris defects	2 (2%)	16 (16.1%)	
	Uveitis	5 (5%)	2 (2%)	
	Acute glaucoma crisis	2 (2%)	10 (10.1%)	
	PES	-	7 (7%)	
Neurological pathologies	Traumatic 3rd CN palsy	4 (4%)	-	-
	Posterior communicating artery aneurysm	2 (4%)	-	
	Intracranial hemorrhage	2 (2%)	2 (2 %)	
	Intracranial mass	-	1 (1%)	
	Nontraumatic 3rd CN palsy	-	1 (1%)	

Discussion

Anisocoria is a clinical finding characterized by unequal pupil size. Anisocoria has a complex etiology ranging from benign causes to life-threatening causes. In our study, the potential etiologies of anisocoria were examined in 4 groups including physiological anisocoria, pharmacological anisocoria, ocular pathologies and pathologies that cause nervous system dysfunction. An attempt was made to determine the most common causes causing anisocoria in individuals aged 18-45 and over the age of 45. In both groups, anisocoria was most frequently caused by ocular pathologies and least by pharmacological agents.

Previous eye surgeries, traumas, iridocyclitis, PES, acute glaucoma crisis, congenital anomalies, benign episodic mydriasis and Adie's tonic pupil are the main ocular causing anisocoria [1]. In our study, while ocular pathologies were the most common cause of anisocoria in both groups, they showed difference in terms of the variety of pathologies. It was found that the iris defects caused by trauma, most frequently in the 18-45 group, caused anisocoria. On the other hand, it was seen that the iris defects occurring secondary to the surgery most frequently caused anisocoria in the group over 45 years of age. While PES was not observed in the 18-45 age group, it is among the most common causes of anisocoria in individuals over the age of 45. Acute glaucoma crisis was seen 5 times more common in individuals over the age of 45 than in the age group of 18-45. Together with aging in the world, limitations and decreases occur in the activities of daily living of individuals and together with advancing age, an increase occurs in the incidence of ophthalmological diseases such as glaucoma, cataract, PES increases [8,9]. Having school and work life in individuals aged 18-45 can lead to a more active life and increase the likelihood of trauma exposure. These reasons explain the differences between the study groups.

Iris dysgenesis such as in coloboma, Axenfeld-Rieger syndrome, and congenital anomalies such as iris cysts can cause anisocoria by creating pupillary irregularity [10,11]. In our study, while anisocoria was detected due to the congenital anomalies in 6 patients aged 18-45 years, anisocoria depending on the congenital anomalies was not observed in any patient over 45 years of age. In acute iridocyclitis, miosis occurs in the pupillary due to iris edema and spasm of the sphincter muscle [12]. In our study, there was anisocoria depending on the iridocyclitis in 5 patients aged 18-45 years and in 2 patients over 45 years of age.

The parasympathetic nervous system causes miosis by activating the iris sphincter via the 3rd CN. These pathways arise in the brainstem and provide pupillary light reflex and accommodation. Pathologies that can occur on this pathway (such as intracranial hemorrhages and herniation, emboli, posterior communicating artery aneurysm) disrupt miosis and can cause anisocoria. In our study, 3rd CN paralysis was observed in 4 patients in the 18-45 age group depending on the trauma, intracranial hemorrhage was observed in 2 patients, and posterior communicating artery aneurysm was observed in 2 patients. In the patient group over 45 years of age, intracranial hemorrhage was observed in 2 patients, intracranial mass was observed in 1 patient, and non-traumatic 3rd CN paralysis was observed in 1 patient.

The sympathetic nervous system is responsible for mydriasis. Sympathetic fibers start from the hypothalamus, makes a synapse at C8-T2 spinal cord level, and extend along the sympathetic chain to synapse with a third neuron in the superior cervical ganglion. The third neurons proceed along the cavernous sinus and innervate the dilator pupillary muscle by entering into orbit [1,13,14]. Any pathology that will be able to affect this pathway (such as internal carotid artery dissection, Horner's syndrome, lung apex tumors, thyroid diseases, cavernous sinus pathologies) can cause deterioration in mydriasis [1]. In our study, no anisocoria due to sympathetic dysfunction was found in either group.

In the literature, the prevalence of physiological anisocoria was reported to be around 10 % to 20% in general, and this rate varies from society to society [15]. The specific gender and age range for the physiological anisocoria has not been reported [16]. Physiological anisocoria was detected in 20 (20.2%) of 99 patients in our study. Eight of them were female and 12 were male.

Pharmacological agents affecting the sympathetic and parasympathetic nervous systems can alter pupil size. In general, drugs taken systemically do not cause anisocoria as both pupils will constitute shrinking or expanding, but these agents can cause anisocoria if administered to only one eye [17]. Nebulized bronchodilators such as ipratropium bromide can cause anisocoria by direct contact [18]. In our study, pharmacological anisocoria was detected in 3 patients treated with ipratropium bromide due to respiratory tract diseases.

Adie's tonic pupil is a well-known cause of anisocoria and is more common in younger women. The diagnosis is made clinically. It is generally rare and its incidence was reported as 0.005% [19]. Benign episodic unilateral mydriasis is another cause of anisocoria. This phenomenon is thought to be related to the imbalance between the sympathetic and parasympathetic nervous systems [20]. In a neuroophthalmological study conducted, the incidence was found to be 0.08% [21]. These two diseases detected rarely were not detected in both patient groups in our study.

Limitations

As far as we know, the studies regarding anisocoria in the literature are found mainly in case reports. The fact that our study is one of the rare studies on the etiology of anisocoria makes our study strong. On the other hand, anisocoria formed in life-threatening situations may have been overlooked and not evaluated due to the need for urgent intervention. We can say that this situation is the most important limitation of our study. On the other hand, we think that we provide valuable information about the ocular causes of anisocoria.

Conclusion

In conclusion, ocular pathologies were found to be the most common cause of anisocoria. The most common ocular causes detected also varied in parallel to demographic changes. While trauma-induced anisocoria was seen in the age group of 18-45, anisocoria depending on the previous surgeries over the age of 45 was seen in the majority. There is a need for descriptive studies of the etiology of anisocoria with higher number of participants.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

The authors declare no conflict of interest.

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